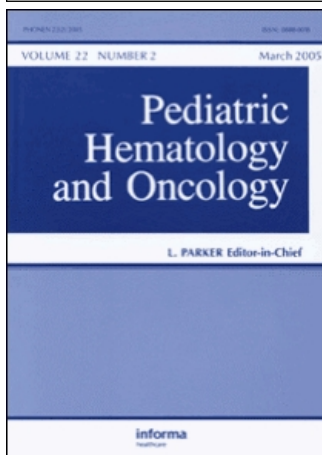


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### HEMOPURE TRANSFUSION IN A CHILD WITH SEVERE ANEMIA

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## Case Report

### HEMOPURE TRANSFUSION IN A CHILD WITH SEVERE ANEMIA

**D. C. Stefan, R. Uys, and G. Wessels** □ *Tygerberg Children's Hospital, Paediatrics and Child Health, Tygerberg, Western Cape Province, South Africa*

□ *A 23-month-old girl presented with heart failure from extremely severe sickle cell anemia. The family refused blood transfusion on religious grounds (Jehovah's Witness). Alternative options acceptable to this religion, such as iron, erythropoietin, or folic acid were rejected as useless in the particular situation of the child. The patient was transfused with Hemopure, a product that consists of polymerized bovine hemoglobin. This is the first case reported in the literature of a child transfused, in an emergency situation, with this product.*

**Keywords** Hemopure, red cell substitutes, sickle cell anemia, acute heart failure, Jehovah's Witness

#### CASE REPORT

A 23-month-old girl was brought by her parents with a short history of vomiting, refusing to eat, and becoming increasingly short of breath. Her family emigrated recently from the Republic of Congo. Several close relatives, including some of her siblings, were already known to have sickle cell anemia. The birth history of this patient was unremarkable and she had not been diagnosed with sickle cell disease before. Immunizations were on schedule and anthropometry, as well as developmental milestones, were age appropriate.

Clinical examination revealed an extremely pale and acutely ill child. Her respiratory rate was 66/min, heart rate 170 beats/min, blood pressure 70/35 mm Hg, and her temperature was normal. Her skin turgor was normal, while the dry tongue and slightly sunken eyes suggested a mild dehydration. The oxygen saturation of the child was 90% in room air.

The child was tachypneic, with intercostal recession and nasal flaring. An examination of the cardiovascular system revealed an ejection systolic murmur of 3/6 intensity and the presence of a gallop rhythm. The spleen

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was grossly enlarged, measuring 9 cm, and the liver was palpable 7 cm below the costal border, with a liver span of 12 cm. She had a reduced level of consciousness with a count of 13/15 on the Glasgow Coma Scale, without meningism, and was irritable when handled.

The initial laboratory investigations showed a Hb of 2 g/dL, a mean corpuscular volume of 101 fL, and white blood cell and platelet counts of  $27 \times 10^9/\text{L}$  and  $44 \times 10^9/\text{L}$ , respectively. Electrolytes were within normal limits. There was no obvious pulmonary pathology on the chest radiograph. The echocardiography showed a dilated left ventricle with supranormal function. The peripheral blood smear showed sickle-shaped red blood cells; the sickling test was positive and the diagnosis was confirmed by hemoglobin electrophoresis.

Management was initiated with the cautious administration of intravenous fluids, with frequent clinical evaluation for worsening signs of heart failure, oxygen, intravenous antibiotics, dobutamine, and low-dose diuretic once the blood pressure normalized. A blood transfusion was urgently necessary but was not accepted by the parents because of religious beliefs (Jehovah's Witness). Alternative treatments were recommended by members of the church, which included the use of iron and erythropoietin. Due to the type of illness and the severity of the situation, these remedies were considered unsuitable.

The only solution appeared to be a transfusion with Hemopure, which was acceptable to the parents. As this hemoglobin-based oxygen carrier is not yet registered for use in children, following emergency internal hospital protocols, approval was sought from two senior consultant pediatricians as well as from the hospital manager. The child received one unit of Hemopure (250 mL with 30–35 g Hb, corresponding to 10 mL/kg body mass) in 3 divided doses over a period of 6 h.

Post-transfusion Hb increased to 4 g/dL. Heart rate decreased to 100 beats/min and blood pressure increased to 100/55 mmHg. The dobutamine was stopped and the child started feeding again. Her liver function tests remained normal; she did not develop jaundice or hypertension, which are known to appear sometimes in conjunction with the use of this product. Her liver size reverted to normal gradually during admission but the spleen remained unchanged.

The child was discharged on penicillin VK, folic acid, and hydroxyurea.

At the follow-up done 2 weeks after discharge she had a Hb of 5.7 g/dL and was clinically well, except for the persistence of the spleen enlargement.

## DISCUSSION

According to our review of the literature it appears that this is the first report of a transfusion of bovine hemoglobin in a child with sickle

cell disease in cardiac failure. Sickle cell disease (SCD) is an autosomal codominant genetic disorder, present in South Africa mainly in migrants originating from Northern and Central Africa; the prevalence of the sickle cell trait in this country is less than 1% [1]. The cause is an abnormal hemoglobin, which produces alterations in the red cell, resulting in a shorter erythrocyte life span.

While heterozygous subjects are usually asymptomatic, homozygotes suffer from increased hemolysis and anemia. This chronic anemia may lead to leg ulcers, bone marrow hyperplasia, poor growth, and delayed maturation. Apart from anemia, hemolysis results in jaundice and gallstones.

Sickle-shaped erythrocytes increase the blood viscosity, which leads to reduced small vessel blood flow with formation of intravascular thrombi. The consequence is painful vasoocclusion in bones, muscle, and abdomen, acute chest syndrome, stroke, eye damage, as well as hypersplenism and splenic blockage; the latter leaves the subject unprotected against bacterial infections. Other consequences may be renal failure and priapism. The only curative treatment is hematopoietic stem cell transplantation. Various non-curative treatments were devised to alleviate the numerous complications enumerated above. Hydroxyurea was used in this patient to stimulate the synthesis of hemoglobin F. In most cases, repeated red cell transfusions are required [2, 3].

A number of red blood cell substitutes have been extensively tested, for indications other than chronic anemia, in the past decade. These are based on hemoglobin, free of red cell membrane (and thus free of associated antigens), polymerized or modified in other ways, to eliminate such issues as coagulopathy, renal compromise, and short intravascular persistence. A wide variety of indications have been studied, ranging from trauma to elective surgery, with transfusion avoidance as the goal. There appears to be an intrinsic side-effect profile associated with this class of drugs, including elevation in blood pressure, abdominal pain, jaundice, and elevations in liver enzymes. These side effects have been mostly classified as minimal to mild. Some studies have shown marked elevations in blood pressure and others increased evidence of troponin leak but no myocardial infarctions. The mechanism of these reactions is thought to be scavenging of nitric oxide by free hemoglobin, resulting in a vasoactive response [4, 5].

Hemopure is a purified cell-free glutaraldehyde cross-linked and polymerized bovine hemoglobin (Hb) in a modified lactated Ringer's solution with  $13 \pm 1$  g/dL Hb, 30–35 g Hb/250 mL unit; pH is 7.6–7.9 and P50 is 40 mm Hg. It can be stored at room temperature for up to 3 years, does not require cross-matching and has a circulating half-life of 19 h. Oxygen release is independent of 2,3-di-phosphoglycerol. It offers an alternative when blood is not available for transfusion or not acceptable to the patient, thus allowing the body the time required to compensate for the anemia [6–8].

Jaundice and hypertension have been reported in adult patients receiving the product. Transient mild increase in plasma liver enzyme levels, as well as lipase levels, may occur after administration but are not associated with clinical hepatitis or pancreatitis.

The product is registered for use in adults in South Africa and is undergoing clinical trials in other countries. There is, however, no information available about the use of this preparation in children. All clinical studies were done in adults with acute surgical anemia. In such cases the use of Hemopure is indicated when blood is not readily available, when it is inappropriate for use due to antibodies or unacceptable to the patient (e.g., on religious grounds).

Hemopure was not developed as a therapeutic agent for use in sickle cell anemia [9]. Typically, this situation would have been managed with an early transfusion of blood. In this case, Hemopure was used, in place of blood, to augment the oxygen-carrying capacity of the blood to improve cardiac perfusion and reverse the ischemic cardiomyopathy associated with the crisis.

We hypothesize that in patients with SCD, by effecting improved tissue oxygenation, Hemopure might work to alleviate the signs and symptoms associated with tissue hypoxia and ischemia associated with the disease. Acting as a bridge to maintain tissue perfusion, it could buy time for other interventions to take hold while interrupting the pathophysiology of the acute complications of SCD. Hemopure might have a place in the therapy of splenic sequestration of erythrocytes, where by increasing the plasma oxygen tension it may limit or reverse the sickling process. Using Hemopure rather than blood in this particular situation, the possible polycythemia that appears when the spleen releases the trapped blood cells might be avoided. Further research is required to verify our assumptions.

For this child with severe anemia and heart failure, Hemopure was the only acceptable therapy available, due to the rejection of the blood transfusion on religious grounds. Our patient had no side effects after the administration of the product. In this case, Hemopure proved to be a clinically efficient and safe oxygen carrier.

In conclusion, this is the first time Hemopure was administered to a child with acute heart failure from severe hemolytic anemia, for which this was the only acceptable therapy. This product may be used as an alternative to blood transfusion in Jehovah's Witness patients. More studies are necessary to establish the safety of the product in children and to determine the correct dose.

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